Document made available under the Patent Cooperation Treaty (PCT)

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P2 1555777

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

January 24, 2007

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***PCT/US03/40518***
FILING DATE: ***December 19, 2003***
RELATED PCT APPLICATION NUMBER: *PCT/US03/41022*

THE COUNTRY CODE AND NUMBER OF YOUR PRIORITY APPLICATION, TO BE USED FOR FILING ABROAD UNDER THE PARIS CONVENTION, IS ***USPCT/US03/40518***

By Authority of the
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

T. Lawrence

T. LAWRENCE
Certifying Officer

PCT/US03/40518

OT12 Rec'd PCT/PTO 19 DEC 2003

TRANSMITTAL LETTER TO THE UNITED STATES RECEIVING OFFICE

Date	12/19/2003
International Application No.	PCT/US03/40518
Attorney Docket No.	P131 WO 01

I. Certification under 37 CFR 1.10 (if applicable)

EL 964154548 US	12/19/2003
Express Mail mailing number	Date of Deposit

I hereby certify that the application/correspondence attached hereto is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop PCT, Commissioner for Patents, PO Box 1450, Alexandria, VA 22313-1450.

Cheryl A. Swanson	Cheryl A. Swanson
Signature of person mailing correspondence	Typed or printed name of person mailing correspondence

II. ☒ **New International Application**

TITLE	A Method and Apparatus for Automatic Staining of Tissue Samples

Earliest priority date (Day/Month/Year)
20/12/2002

SCREENING DISCLOSURE INFORMATION: In order to assist in screening the accompanying international application for purposes of determining whether a license for foreign transmittal should and could be granted and for other purposes, the following information is supplied. (Note: check as many boxes as apply):

A. ☐ The invention disclosed was **not** made in the United States.

B. ☐ There is no prior U.S. application relating to this invention.

C. ☒ The following prior U.S. application(s) contain subject matter which is related to the invention disclosed in the attached international application. *(NOTE: priority to these applications may or may not be claimed on form PCT/RO/101 (Request) and this listing does not constitute a claim for priority.)*

application no.	US 60/435,601	filed on	20/12/2002 (20 December 2002)
application no.		filed on	

D. ☒ The present international application contains additional subject matter not found in the prior U.S. application(s) identified in paragraph C. above. The additional subject matter is found on pages [all text, headings, andabstract]

and ☐ **DOES NOT ALTER** ☒ **MIGHT BE CONSIDERED TO ALTER** the general nature of the invention in a manner which would require the U.S. application to have been made available for inspection by the appropriate defense agencies under 35 U.S.C. 181 and 37 CFR 5.1. See 37 CFR 5.15.

III. ☐ **A Response to an Invitation from the RO/US.** The following document(s) is (are) enclosed:

A. ☐ A Request for An Extension of Time to File a Response

B. ☐ A Power of Attorney (General or Regular)

C. ☐ Replacement pages:

pages		of the request (PCT/RO/101)	pages		of the figures
pages		of the description	pages		of the abstract
pages		of the claims			

D. ☐ Submission of Priority Documents

Priority document		Priority document	

E. ☐ Fees as specified on attached Fee Calculation sheet form PCT/RO/101 annex

IV. ☐ **A Request for Rectification under PCT 91** ☐ **A Petition** ☐ **A Sequence Listing Diskette**

V. ☒ **Other** (please specify): Request Form including the specification, claims, abstract, and drawings, Powers of Attorney, Powers of Agent, firm letter of transmittal, a check in the amount of $ 2136.00, Certificates of Express Mailing for each document, and a return post card

The person signing this form is the:	☐	Applicant	Nicole Ressue
	☒	Attorney/Agent (Reg. No.) 48,665	Typed name of signer
	☐	Common Representative	Nicole Ressue
			Signature

HOME COPY

PCT

PCT/US03/40518 Express Mail No. EL 964154548 US

For receiving Office use only

International Application No. PCT/US03/40518

International Filing Date (19.12.03) 19 DEC 2003

PCT INTERNATIONAL APPLICATION DOMUS

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* P131 WO 01

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

Box No. I TITLE OF INVENTION

A Method and Apparatus for Automatic Staining of Tissue Samples

Box No. II APPLICANT ☐ This person is also inventor

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DAKOCYTOMATION DENMARK A/S
Produktionsvej 42
DK-2600 Glostrup
DK

Telephone No. 45 44 85 93 36

Facsimile No. 45 44 85 84 32

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: DK

State *(that is, country)* of residence: DK

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SWEET, Doug
117 Cannon Drive
Santa Barbara, CA 93105
US

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RESSUE, Nicole
Santangelo Law Offices, P.C.
125 South Howes, Third Floor
Fort Collins, CO 80521
United States of America

Telephone No. (970) 224-3100

Facsimile No. (970) 224-3175

Teleprinter No.

Agent's registration No. with the Office 48,665

☒ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III **FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KEY, Mark
290 Saddle Lane
Ojai, CA 93023
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FEINGOLD, Gordon
5242 Austin Road
Santa Barbara, CA 93111
YS

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BUCHANAN, Kristopher
4300 Shadowbrook Court
Fort Collins, CO 80526
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

LATHROP, Bob
1667 Glenrock Court
San Jose, CA 95124
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

 PCT/US03/40518

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FAVUZZI, John
5086 San Bernardo Place
Santa Barbara, CA 93111
US

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **MZ** Mozambique, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZM** Zambia, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **#2 European Patent:** **AT** Austria, **BE** Belgium, **BG** Bulgaria, **CH & LI** Switzerland and Liechtenstein, **CY** Cyprus, **CZ** Czech Republic, **DE** Germany, **DK** Denmark, **EE** Estonia, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **HU** Hungary, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **RO** Romania, **SE** Sweden, **SI** Slovenia, **SK** Slovakia, **TR** Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GQ** Equatorial Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates	☒ **HR** Croatia	☒ **OM** Oman
☒ **AG** Antigua and Barbuda	☒ **HU** Hungary	☒ **PG** Papua New Guinea
☒ **AL** Albania	☒ **ID** Indonesia	☒ **PH** Philippines
☒ **AM** Armenia	☒ **IL** Israel	☒ **PL** Poland
☒ **AT** Austria and utility model	☒ **IN** India	☒ **PT** Portugal and utility model
☒ **AU** Australia ... #3.	☒ **IS** Iceland	☒ **RO** Romania
☒ **AZ** Azerbaijan	☒ **JP** Japan .. #5.	☒ **RU** Russian Federation
☒ **BA** Bosnia and Herzegovina	☒ **KE** Kenya	
☒ **BB** Barbados	☒ **KG** Kyrgyzstan	☒ **SC** Seychelles
☒ **BG** Bulgaria	☒ **KP** Democratic People's Republic of Korea	☒ **SD** Sudan
☒ **BR** Brazil		☒ **SE** Sweden
☒ **BY** Belarus	☒ **KR** Republic of Korea	☒ **SG** Singapore
☒ **BZ** Belize	☒ **KZ** Kazakhstan	☒ **SK** Slovakia and utility model
☒ **CA** Canada #4	☒ **LC** Saint Lucia	☒ **SL** Sierra Leone
☒ **CH & LI** Switzerland and Liechtenstein	☒ **LK** Sri Lanka	☒ **SY** Syrian Arab Republic
☒ **CN** China	☒ **LR** Liberia	☒ **TJ** Tajikistan
☒ **CO** Colombia	☒ **LS** Lesotho	☒ **TM** Turkmenistan
☒ **CR** Costa Rica	☒ **LT** Lithuania	☒ **TN** Tunisia
☒ **CU** Cuba	☒ **LU** Luxembourg	☒ **TR** Turkey
☒ **CZ** Czech Republic and utility model	☒ **LV** Latvia	☒ **TT** Trinidad and Tobago
☒ **DE** Germany and utility model	☒ **MA** Morocco	
☒ **DK** Denmark and utility model	☒ **MD** Republic of Moldova	☒ **TZ** United Republic of Tanzania
☒ **DM** Dominica		☒ **UA** Ukraine
☒ **DZ** Algeria	☒ **MG** Madagascar	☒ **UG** Uganda
☒ **EC** Ecuador	☒ **MK** The former Yugoslav Republic of Macedonia	☒ **US** United States of America .. #1.
☒ **EE** Estonia and utility model		
☒ **ES** Spain	☒ **MN** Mongolia	☒ **UZ** Uzbekistan
☒ **FI** Finland and utility model	☒ **MW** Malawi	☒ **VC** Saint Vincent and the Grenadines
☒ **GB** United Kingdom	☒ **MX** Mexico	☒ **VN** Viet Nam
☒ **GD** Grenada	☒ **MZ** Mozambique	☒ **YU** Serbia and Montenegro
☒ **GE** Georgia	☒ **NI** Nicaragua	☒ **ZA** South Africa
☒ **GH** Ghana	☒ **NO** Norway	☒ **ZM** Zambia
☒ **GM** Gambia	☒ **NZ** New Zealand	☒ **ZW** Zimbabwe

☒ all possible states & all possible countries that have become members of the PCT since issuance of this form

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ .BW Botzswana ☒ .EG Egypt ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 20 December 2002 (20.12.02)	60/435,601	US		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / US .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following **declarations** are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐	Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application **contains:**

(a) **in paper form,** the following number of sheets:

request (including declaration sheets)	:	6
description (excluding sequence listings and/or tables related thereto)	:	25
claims	:	8
abstract	:	1
drawings	:	5
Sub-total number of sheets	:	45
sequence listings	:	
tables related thereto	:	
(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)		
Total number of sheets	:	45

(b) ☐ **only in computer readable form** (Section 801(a)(i))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

(c) ☐ **also in computer readable form** (Section 801(a)(ii))
- (i) ☐ sequence listings
- (ii) ☐ tables related thereto

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the
- ☐ sequence listings: .....
- ☐ tables related thereto: .....

(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)

This international application is **accompanied by** the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item):*

		Number of items
1. ☒ fee calculation sheet	:	1
2. ☒ original separate power of attorney and 6 Powers of Agent	:	7
3. ☐ original general power of attorney	:	
4. ☐ copy of general power of attorney; reference number, if any:	:	
5. ☐ statement explaining lack of signature	:	
6. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into *(language)*:	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listings in computer readable form *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (c)(i) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column	:	
10. ☐ tables in computer readable form related to sequence listings *(indicate type and number of carriers)*		
(i) ☐ copy submitted for the purposes of international search under Section 802(b-*quater*) only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(ii) or (c)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-*quater*)	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column	:	
11. ☒ other *(specify)*: Letter of Transmittal; Express Mail; ..... Certificates for each document; USRO Letter of Transmittal	:	

Figure of the drawings which should accompany the abstract: 1

Language of filing of the international application: English

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

Nicole Ressue

Nicole Ressue, #48,665

December 19, 2003

Date

(19.12.03)

For receiving Office use only

1. Date of actual receipt of the purported international application: PT12 Rec'd PCT/PTO 19 DEC 2003

2. Drawings:
- ☐ received:
- ☐ not received:

3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:

4. Date of timely receipt of the required corrections under PCT Article 11(2):

5. International Searching Authority (if two or more are competent): ISA / US

6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only
International Application No. PCT/EP 03/ 40518
Date stamp of the receiving Office (19.12.03)

Applicant's or agent's file reference: P131 WO 01

Applicant: DakoCytomation Denmark A/S

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE	240.00 T	240
2. SEARCH FEE	700.00 S	700
International search to be carried out by: US		
(If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)		
3. INTERNATIONAL FEE		
Basic Fee		
Where items (b) and/or (c) of Box No. IX apply, enter **Sub-total number of sheets** Where items (b) and (c) of Box No. IX do not apply, enter **Total number of sheets**		
b1 first 30 sheets	476.00 b1	476
b2 15 (number of sheets in excess of 30) x 12.00 (fee per sheet) =	180.00 b2	180
b3 additional component (only if sequence listings and/or tables related thereto are filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):		
400 x ____ (fee per sheet) =	b3	
Add amounts entered at b1, b2 and b3 and enter total at B	656.00 B	656
Designation Fees		
The international application contains all designations.		
5 (number of designation fees payable *(maximum 5)*) x 104.00 (amount of designation fee) =	520.00 D	520
Add amounts entered at B and D and enter total at I	1176.00 I	1,176
(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)		
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(for an international application filed under the Patent Cooperation Treaty)
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to represent the undersigned before

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__ the International Searching Authority only

__ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of invention: A Method and Apparatus for Automatic Staining of Tissue Samples

Applicant's or agent's file reference: P131 WO 01

International application number (if already available):

filed with the following Office USPTO as receiving Office and to make or receive payments on behalf of the undersigned. Further, I grant the above persons and entities, the power to insert on any document filed in this matter any further identification which may be necessary or desirable in order to indicate filing information or to comply with the rules of the United States Patent Office or any foreign patent office for recordation of this document, including, but not limited to, inserting the application number, the execution date, mailing information, or the filing date of the above-identified United States Patent Application based upon the invention.

Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading the request or this power):

Jes Ostergaard
Title: President / CEO

Dec 15, 2003
Date:

Form PCT/Model of power of attorney (for a given international application) (July 1992)

Express Mail No.: EL 964154548 US

PCT

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in connection with the international application identified below:

Title of invention: Systems and Methods of Sample Processing and Temperature Control

Applicant's or agent's file reference: P139 WO 01

International application number (if already available):

filed with the following Office: USPTO as receiving Office and to make or receive payments on behalf of the undersigned. Further, I grant the above persons and entities, the power to insert on any document filed in this matter any further identification which may be necessary or desirable in order to indicate filing information or to comply with the rules of the United States Patent Office or any foreign patent office for recordation of this document, including, but not limited to, inserting the application number, the execution date, mailing information, or the filing date of the above-identified United States Patent Application based upon the Invention. The undersigned acknowledges that the agent(s) appointed is/are attorneys for the assignee only.

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Title of invention: A Method and Apparatus for Automatic Staining of Tissue Samples

Applicant's or agent's file reference: P131 WO 01

International application number (if already available):

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Marc Key Date: 12/19/03

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in connection with the international application identified below:

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Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs; if such capacity is not obvious from reading the request or this power):

Date: 12/19/2003

FEINGOLD, Gordon
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in connection with the international application identified below:

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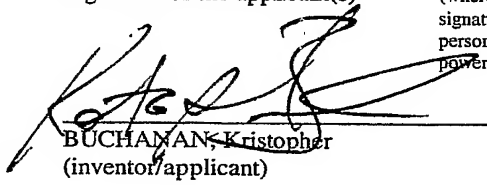
Signature of the applicant(s) (where there are several applicants, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs; if such capacity is not obvious from reading the request or this power):



Date: 19 Dec 03

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Title of invention: A Method and Apparatus for Automatic Staining of Tissue Samples

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in connection with the international application identified below:

Title of invention: A Method and Apparatus for Automatic Staining of Tissue Samples

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FAVUZZI, John
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A METHOD AND APPARATUS FOR AUTOMATIC STAINING OF TISSUE SAMPLES

TECHNICAL FIELD

The present invention relates to an apparatus and a method for automatic staining of tissue samples. It may further relate to systems for sample processing and data acquisition, data maintenance, and data retrieval for sample processing. Applications to which the present invention may especially relate include immunohistochemistry, in-situ hybridization, fluorescent in-situ hybridization, special staining, and cytology, as well as potentially other chemical and biological applications.

BACKGROUND

Tissue sample processing in immunohistochemical (IHC) applications and in other chemical and biological analyses, such as in-situ hybridization, special staining and cytology, may require one or more processing sequences or protocols as part of an analysis of one or more samples. The sample processing sequences or protocols may be defined by the individual or organization requesting an analysis, such as a pathologist or histologist of a hospital, or may be defined by dictates of a particular analysis to be performed, e.g. standardized protocols defined by an organization.

In preparation for sample analysis, a biological sample may be acquired by known sample acquisition techniques and may comprise tissues which in some applications may even be one or more isolated cells. The tissue sample may be accommodated on a sample carrier such as a slide or perhaps a microscope slide.

For example, immunologic applications may require processing sequences or protocols that comprise steps such as deparaffinisation, target retrieval, and staining. Previously, in some applications, these steps may have been performed manually,

potentially resulting in a time consuming protocol and necessitating personnel to be actively involved in sample processing. In particular relating to the staining process, various devices for automated staining of tissue slides are known, as attempts have been made to automate sample processing to address the need for expedient sample processing and less manually burdensome operation.

Aspects of the present invention may be especially applicable to sample processing having one or a plurality of processing steps to be performed on one, a portion, or an entirety of samples, such protocols identified in some instances by the individual carriers presenting the samples. Aspects of the present invention may be especially applicable to immunohistochemistry (IHC) techniques, as well as in-situ hybridization (ISH) and fluorescent in-situ hybridization (FISH), especially techniques incorporating the staining of samples.

Embodiments of the invention may further relate to automated control systems for sample processing. Embodiments may also be directed to data acquisition, data maintenance, data retrieval for sample processing, especially information sharing of processing protocol and processing status, such as for individual samples or multiple batch processing, sample diagnostic features, and real-time or adaptive capabilities for multiple batch processing.

US 5,839,091 discloses an apparatus for automatic tissue staining where microscope slides are arranged in a number of rows and reagent vials are stored in a section next to this slide section. A robotic head picks up a predetermined amount of reagent from a bottle and deposits this amount of reagent on a predetermined slide and blows the liquid off the slides according to a control program. This program is run on a computer that is coupled to the staining apparatus. The apparatus is loaded with a number of slides, and each slide and its position is registered in the computer and a staining sequence is selected. The program also receives data relating to the reagents and their position in the reagent section. On the basis of these slide and reagent

position data, the program calculates a staining run and controls the robotic motion in the apparatus.

US 6,352,861 discloses a carousel-type automatic staining apparatus in which the slides are arranged on a rotatable carousel slide support and the reagents are similarly arranged on a rotatably carousel reagent support above the slide support. A particular slide is then rotated to a delivery zone and a particular reagent vial is also rotated to this position and reagent is dispensed onto the slide. The slides and the reagent bottles are provided with bar codes and associated bar code readers are provided to identify the slides and the reagents respectively. A blowing zone and an identifying zone are also provided at the periphery of the slide carousel. The slide bar codes identify the slide samples and their particular immunohistochemical processes required for the particular samples. A reagent bar code reader is positioned to scan the reagent bar codes on the reagent bottles. The scanned information from the slide bar code reader and the reagent bar code reader is fed into a computer and correlated with the indexed position of the slide and the reagent carousel, respectively. This information is used to rotate the slide carousel and the reagent carousel to place the correct reagent bottle in the dispense zone for each slide treatment step for each slide.

A drawback of the automated staining apparatus described in '091 is that the position of each of the tissue slides and each of the reagent vials in the slide section and in the reagent section, respectively, must be entered manually into the computer, since the control program cannot check the location of the particular slides and reagent vials. This involves the risk that a misplaced slide is treated with the wrong staining protocol and makes the apparatus very inflexible in use.

Although the '861 patent uses a bar code identification of the slides and reagents, this carousel-type apparatus is time consuming in running the staining protocols, since this involves rotating the carousels with the entire reagent inventory and the slide carousel with all the slides for each step in a protocol. These rotations are time

consuming and make this type of apparatus unsuitable for running of larger numbers of slides. Moreover, the bar codes can only carry a small amount of data, typically simply an identification code, which means that the control computer must be provided with corresponding data associated with the identification codes.

DISCLOSURE OF INVENTION

It is an object for the present invention to provide an automatic tissue sample processing apparatus of the initially mentioned kind, with automatic identification of the inventory of reagents and slides present in the machine. Another object is to provide identification of relevant properties of the apparatus to allow for automatic preparatory checks before a staining process of newly loaded slides is initiated.

In one embodiment these objects are achieved by an apparatus of the initially mentioned kind wherein a robotic element, perhaps with a robotic head, is provided with an optical sensor, or perhaps a 2-D optical sensor means for detecting two-dimensional image data of a relevant property and with the capability of feeding the captured image data to the control means.

The invention also provides a method of identifying at least one property in an automatic staining apparatus perhaps including at least one slide array and a reagent array and a robotic element or perhaps robotic means for performing staining of the slides also using reagents;

said method including in one embodiment the steps of

providing optical sensor means on the robotic head of the robotic means,

moving the optical sensor means on said robotic head to a predetermined position,

recording relevant image data at said position, and

feeding said image data to a control system for manipulating the staining process according to said image data.

Furthermore, the invention concerns a method of staining tissue samples in an automatic staining apparatus perhaps including at least one slide array and a reagent array, a robotic element or perhaps and robotic means for performing staining of the slides also using reagents according to tissue sample specific staining protocols; said method including in one embodiment the steps of:

providing optical sensor means on the robotic head of the robotic means,

moving the optical sensor means on said robotic head to a predetermined position,

recording relevant image data at said position by said optical sensor means;

feeding said image data to a control system for manipulating the staining process according to said image data; and

staining a tissue sample also using reagent from a reagent container.

In embodiments, the automatic staining apparatus 1, that is any apparatus that stains with at least some automated operation, may include a reagent container 3. One or more reagent containers 3 may be positioned in a reagent section 2 of the automatic staining apparatus 1. The automatic staining apparatus may also include a tissue sample 74 which may therein be placed on a slide. A plurality of slides with tissue samples thereon may also be positioned in a slide section 5 of the automatic staining apparatus 1. The invention, in embodiments, may also include a robotic element 20, some type of control element, and even an optical sensor (86), perhaps an image-capture 2-D optical sensor. As can be easily understood, the control element 85, may be a computer, software routine, or merely a particular programmable processor functionality.

As mentioned, the present invention may provide for the capability of optically sensing a two dimensional image. This can occur through an image-capture 2-D sensor which may provide a two-dimensional image of an element in the auto staining apparatus 1. Through providing the robotic element or perhaps a robotic head with a 2-D optical sensor or means, as but one embodiment, a common image processing means is able to have multiple functions. By using a 2-D optical image processing system, the control system of the apparatus may easily be adapted to read various types of data presentations, just as actual images of elements or for sections of the apparatus may be identified in order to assess the condition of the apparatus. The optical sensor or optical sensor means may be used to automatically identify the slides and the reagent containers present in the apparatus, just as the optical sensor or optical sensor means may be used for checking if a slide is misplaced at or absent from a certain slide position, etc.

An optical sensor provides a staining apparatus according to the invention with a hitherto unseen flexibility and possibility of automating the identification functions in a staining apparatus. By utilizing a CCD-camera or the like, perhaps on the robotic head or even the robotic element, individual identification means for each of the identification tasks may no longer be required. This means that controlling as well as maintenance of the apparatus is facilitated. The software controlling the apparatus may be adapted to include automated identifications of various properties and conditions of the apparatus, including slide and reagent information. By a method of identifying relevant properties in the staining apparatus and a method of performing the staining process according to the invention, the automated staining process may be less time-consuming and more qualitative checks may be included without loosing any significant speed in the slide staining operations.

In one embodiment of the invention, the reagent section accommodates a plurality of reagent containers stationary arranged in a plurality of rows. Similarly, the tissue samples are accommodated on slides that are stationary arranged in a plurality of

rows in the at least one staining section or slide section during the staining process. The layout of these sections is such that it presents a substantially planar platform work area for the robotic head, which is moveable in the X and Y-axis. In a particularly preferred embodiment, a row of slides and/or reagents can be removed and be replaced without interfering with the staining process.

In another preferred embodiment, the apparatus comprises at least two staining sections separated by a reagent section, that is they may be arranged so that at least some of the tissue samples are closer to at least some of the reagent containers. Hereby, the movements required by the robotic head in order to reach all the slides may be significantly limited and the capacity of the staining apparatus can hereby be increased, just as a reduction in the time for running the staining protocols or other advantages may be achieved. It is further realized that these shorter processing times or other advantages may also be achieved by this layout of the slide and reagent sections without a vision system, e.g. an optical sensor.

In other preferred embodiments of the invention, the optical sensor may be a camera or perhaps include a CCD element. By the term "camera" it should be understood that any image capture apparatus is intended whether or not is uses film, plates, memory, or any type of electronic media and whether or not it images light, visible electromagnetic radiation, or even non-visible electromagnetic radiation such as now well known. By recording the relevant image, relevant image data, or even recording digital image data, a computer processing of this data in the control system may be carried out in a quick manner by known image processing capabilities already available. Moreover, by using this digital technology relative complex images can be recorded with high resolution, just as a fast recording of several identifications, e.g. labels on an entire row of slides, may be achieved as the robotic head may be moved across the slide labels in a continuous movement, so stop and start time for each slide identification may be avoided. However, by the invention it is realized that other

image sensors, e.g. solid state sensors, or perhaps CMOS sensors could also be used depending on the requirements for image resolution.

As indicated above, the optical sensor may be adapted to record the individual reagent containers or bottles and slides present in the apparatus. While of course it may image larger areas, or perhaps even the entire device, it may be configured for individual imaging either electronically, optically, or positionally. Regardless, as a result of the imaging capability, predetermined positions of the slides or reagent containers or bottles that are loaded into the automatic staining apparatus may not be required, since the apparatus may be adapted to automatically identify new slides and reagent bottles once they are loaded into the apparatus.

In an embodiment, the reagent containers and the slides may be provided with an optical identification element. For example, a reagent container may be provided with a reagent optical identification element and a slide may be provided with a slide optical identification element. These optical identification elements may contain machine readable data concerning the reagent type as well as other relevant data relating to the reagent in the bottle, and the slide identifiers may contain data concerning the tissue sample, such as identification of the patient, the staining protocol, etc. An optical identification element may include reiterated information or perhaps even redundant information. This may include information that is repeated or even partially repeated and may even include information that may or may not be in different versions which may relate to similar information.

The optical identification element or alternatively optical identification means may be on or even mounted on the reagent container or on the slides in such a manner that the optical identification element is readable by the optical sensor. By being positioned "on" it is intended that any manner of association be encompassed; thus it should be understood that separate attachment or surface mounting is not required. Similarly, by being "above" it should be understood that this may exist not only in a

sense such as with respect to gravity, but also in a figurative sense such as roughly perpendicularly above a surface or the like. In an embodiment, the optical identification element may be readable from above by the optical sensor or alternatively means. Furthermore, the optical identification element may be provided on a label, which is perhaps adhesively attachable to a specific slide or reagent bottle. Hereby, the labels or perhaps adhesive labels may be presented to the optical sensor means on the robotic head above the slides and the reagent bottles facilitating the reading of the optical identification means. By providing the optical identification means on a printed label which is attached to the slide, respectively the reagent bottle, individual labels may be prepared on site and the relevant data may be entered into a computer and a corresponding label carrying said relevant data may be printed on an associated label printer.

In an embodiment of the invention, one type of optical identification element may be a two-dimensional high-resolution symbology code, e.g. of the so-called "Infoglyph™" type. The optical identification may also be more generically a two-dimensional symbology. Two-dimensional symbology may be representative of data including, but not limited to: tissue sample related data, patient identification data, staining protocol data, reagent related data, reagent type data, reagent volume related data, reagent durability related data, and the like data. By encoding the relevant information into numerous tiny, individual graphic elements, typically small lines in 45° diagonal lines as short as 0.02 mm (1/100 inch), a high resolution with high contrast encoded information label may be achieved which is printable in a printer and readable by a high resolution camera. The type of encoded 2-D symbology label may be provided in different colors and in a variety of materials.

Alternatively, the optical identification means or alternatively the optical identification element may be a data matrix code or even a one-dimensional bar code, namely the identification code with a pattern of vertical bars whose width and spacing identifies an item marked. An advantage of using an optical sensor capable

of reading 2-D symbology is that the apparatus may be capable of reading any kind of optical identifier, as this is only requires an adaptation in the software processing the captured perhaps digital image.

In an embodiment, an optical identification element label may include a two-dimensional (2-D) symbology zone and even at least one human readable text zone, each as conceptually depicted in Fig. 5. Hereby, an extra visual inspection of the label by the operator may be provided for verification of the printed label.

In a more advanced usage of the 2-D image capturing capability, the image processing capability or image processor element may be adapted to identify the texture or outline of the tissue sample itself captured by the optical sensor and may use said image-captured tissue property as an individual identification of the tissue sample. The optical sensor may be configured to identify desired features of the tissue samples such as but not limited to the texture, outline, a visual property, or even an individual feature of a tissue sample. Of course, various different features or properties may be identified as desirable to detect or perhaps identify, a property which may include any attribute, characteristic, or the like. This embodiment could make the use of slide labels obsolete, as the tissue texture itself or at least a predefined section thereof (with or without magnification) could be used as an identifier for a list of data in the control software.

In one preferred embodiment of the invention, the optical sensor may be a moveable optical sensor which may be moveable along the areas above the staining and the reagent sections, and said optical sensor may be adapted to determine the presence of and the positions of slides in the at least one staining section. This may be facilitated by having the optical sensor movable in response to or perhaps on a robotic element. Once a new set of slides are being loaded into the apparatus, this feature would allow the staining apparatus according to this embodiment of the invention to automatically determine where the slides are positioned so that the optimal scheduling of treatment

steps can be calculated. The optical sensor may even determine the approximate location and the approximate area of a tissue sample. Furthermore, this capability may also provide the apparatus control software with warning if a slide is not correctly positioned or other irregularities have occurred during the loading of the slides.

In another embodiment of the invention, the optical sensor may be adapted to locate pre-selected reference locations for self-calibration of the robotic control system or robotic element controlling the movements of the robotic head. The camera can be used to teach the robotic arm critical locations necessary to calibrate the system, allowing the apparatus to properly position the robotic head to all required positions and locations within the platform work area. If the apparatus has been moved or otherwise been tampered with, e.g. due to maintenance, etc., this feature may provide the staining apparatus according to the invention with the capability of self-calibrating the robotic motion control system, e.g. if the slides are arranged in racks (intended to broadly encompass any locationally tied collection) by checking if the slide rack fit correctly into a receiving element in the apparatus, and/or by determining the position of predefined reference components of the apparatus.

In another embodiment of the invention, the optical sensor may be a camera adapted to record an image of the finalized tissue sample after said tissue sample has been subjected to a staining protocol for recording an image of the manipulated tissue sample. Hereby, a picture or digital image of the stained tissue sample may be recorded, preferably in a high resolution, for later examination or for sending this digitalize picture to a remote location for examination. Accordingly, in embodiments the present invention may provide for storing an image relevant to the process of staining tissue samples. This may include images both before and after staining or some other operation, of course. Also, this feature of the invention may provide for archiving images of the about to be stained or the stained tissue samples for later verification of the tissue sample analysis or the identification if this should it be

required. Thus the invention may automatically facilitate a user activity such as those mentioned. To understand the various possibilities, the automatic facilitation may be of activities including, but not limited to, later accessing a historical image of a stained tissue sample, remotely accessing an image of a stained tissue sample, archiving an image of a stained tissue sample, later accessing a historical image of an unstained tissue sample, remotely accessing an image of an unstained tissue sample, archiving an image of an unstained tissue sample, and the like activities.

A sensor may be provided in some embodiments that may automatically identify information from one or more slides or reagent containers. In some embodiments, protocol information may be provided by the adaptive sample processing control system. The sample processing system may process one or more slides, or one or more batches of slides, concurrently, sequentially, or in any other temporal fashion, potentially in accordance with protocol information provided by a slide having a sample or provided by the adaptive sample processing control system. Sample batches or individual slides may be inserted or removed during processing protocol steps by the control and monitoring accomplished by the adaptive sample processing control system.

Another embodiment of the present invention that may achieve the foregoing and other objects of invention may comprise a method of sample processing, comprising the steps of: accessing at least one of a plurality of drawers, providing at least one sample carrier retainment assembly configured with at least one sample carrier, configuring at least one of the drawers with the at least one sample carrier retainment assemblies, and adaptively processing the sample carriers. The step of adaptive processing may automate the processing of samples and may allow for either or both continuous or batch processing of slides, and may afford multiple independent slide processing and in some embodiments redundant slide processing to process each slide independently.

Embodiments of the invention may further comprise a method of automated sample processing, comprising the steps of: acquiring protocol information, transmitting the protocol information to at least one sample processing system, adaptively processing samples, and acquiring sample processing information from the step of adaptively processing. Furthermore, embodiments may provide: maintaining the protocol information, maintaining the sample processing information, information sharing of protocol information, and sample processing information. These and other method steps may be provided for individual samples or multiple batch processing, sample diagnostic features, and real-time or adaptive capabilities for multiple batch processing.

Many aspects of invention are applicable to immunohistochemistry (IHC) techniques, as well as in-situ hybridization (ISH) and fluorescent in-situ hybridization (FISH) special staining of samples, and microarrays, especially techniques incorporating target retrieval or the staining of samples.

Support should be undersood to exist for the following aspects and embodiments of the invention:

An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive; and

an image-capture 2-D optical sensor configured to two dimensionally image at least one element in said automatic staining apparatus.

A method of identifying at least one property in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

optically sensing a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data; and

feeding said image data to a control element to which said robotic element is responsive.

A method of staining samples in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

providing an optical sensor responsive to said robotic element and adapted to sense a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data; and

feeding said image data to a control element to which said robotic element is responsive.

An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive; and

a multifunction optical sensor configured to sense at least one element in said automatic staining apparatus.

BRIEF DESCRIPTION OF DRAWINGS

In the following the invention is described with reference to the accompanying drawings, in which:

Fig. 1 is a schematic perspective view of a staining apparatus according to the preferred embodiment of the invention;

Fig. 2 is a top view of the work area in the staining apparatus shown in fig. 1;

Fig. 3 is a detailed view of the robotic element in the staining apparatus according to some embodiments of the invention;

Fig. 4 is a top view of a reagent bottle with optical identification means;

Fig. 5 is a microscope slide with an optical identifier label thereon;

Fig. 6 is an example of a lay-out of this label; and

Figs. 7 to 10 are examples of various kinds of optical identifying means on the slides.

MODE(S) FOR CARRYING OUT THE INVENTION

An automatic staining apparatus 1 according to the invention is shown in figures 1 and 2. The automatic staining apparatus 1 comprises a rectangular frame 4 surrounding a reagent station or section 2 comprising an array of reagent bottle or container compartments, wherein each compartment a reagent vial or reagent container 3 is placed, and a first and second slide sections 5 wherein a number of separate racks 6 is placed, and where each rack 6 comprises a number of microscope slides 7 mounted side by side in the rack 6. A plurality of reagent containers or even slides may be placed in any desired order, an array. In the embodiment shown, each rack may hold up to 8 slides, but the rack may be designed to hold any suitable number of slides. With eight racks arranged side by side, the shown embodiments may hold up to 64 slides 7 each having a sample, e.g. a tissue mounted on the upper side of the slide, so that reagent may be applied from above to the sample on each slide. The sample processed may be any material, but is most likely a biologic

material such as a biological sample or a biological specimen, perhaps such as a histological sample, e.g. tissue and cell specimens, cells, collections of cells, or tissue samples, the definition to include cell lines, proteins and synthetic peptides, tissues, cell preps, cell preparations, blood, bodily fluids, bone marrow, cytology specimens, blood smears, thin-layer preparations, and micro arrays. It should also be understood to include slide-based biological samples.

As mentioned, the present invention may include a robotic element, which may somehow affect the reagent container and tissue sample. Thus any sort of action to, action resulting from, or merely information from the reagent container or tissue sample may be facilitated through the robotic element. The robotic element, in embodiments, may be adapted to perform staining of the slides with (including as a result of or in conjunction with) the reagent application or the like. The robot arm or robotic element 20 may also remove reagent from a reagent container to a predetermined tissue sample. For example, a robotic element 20 for moving a probe 10 in X and Y (as well as Z) direction as indicated by the arrows X and Y is arranged above the frame 4 of the staining apparatus. A robot arm may position the probe 10 above all reagent vials 3 as well as above all the slides 7, and may further operate the probe 10 to aspirate portions of reagent contained in any of the vials 3, to transfer the portion of reagent and apply it to any of the slides 7 in order to provide a selected staining or treatment of the sample on each slide 7. A control element may manage a staining process by controlling the entire process or even any portion of it. By use of a suitable control element or alternatively a control means e.g. capability within a computer (not shown) having the appropriate software and input data for the purpose, this staining apparatus 1 may be able to automatically stain or treat samples requiring different staining or treatment reagents and processes.

As shown in fig. 1 and 3, the probe 10 is accommodated in a robotic head 22 and is manipulated by the robotic element 20. The probe 10 is raised to an upper position (in a Z direction) where it is clear of the vials 3 underneath the probe 10, but the robot may include means or element in the robotic head 22 for lowering the probe 10 in order to dip the probe tip into the content of a selected reagent vial 3 and to

aspirate a selected amount of reagent for the selected staining or treatment process. In an embodiment, the present invention may include providing an optical sensor 86 on a robotic element and perhaps moving the optical sensor to a predetermined position through action of the robotic element. As but one example, the robotic head 22 may be provided with an optical sensor 86, perhaps even a CCD camera 25 pointing downwards. An optical sensor may be positioned on or perhaps more broadly in response to the robotic element. After the optical sensor is positioned, image data may be recorded at the location at which the optical sensor is established.

In some embodiments a robotic element 20 or even a robotic head 22 may include a variety of components, including but not limited to a push tool 38 that may be connected to an air cylinder 39, a probe 10 that may be responsive to a probe movement element 36 which may even be connected to a syringe pump 37, and an optical sensor 86 as shown in Figure 3.

In embodiments, the optical sensor may detect two-dimensional image data of a relevant property. It may also be adapted to sense a two-dimensional image of an element in general. The camera may be utilized to determine status information of the slides and the reagent bottles and other features of the apparatus in the work area, for example reading a code provided on a reagent container to determine the reagent type and the reagent location within the system. The camera may also determine status of the tissue sample carriers, for example the location of a particular slide, informational indicia, such as a code, that indicate information about the tissue sample presented on the slide or the processing protocol to be performed. A camera may be used for diagnostic purposes. In some embodiments, the sample may be scanned for further analysis, potentially by a computer. The present invention may include, in embodiments, a computer image biological analysis element or perhaps even biologically analysing image data of a sample with a computer.

As previously discussed, the invention may include recording a variety of relevant image data. Of course, a variety of relevant image data may be recorded.

Importantly, this may include recording element calibration reference points, or perhaps even robotic element calibration reference positions on or in the apparatus. As mentioned, the invention may also provide for recording slide identification image data and reagent identification image data. A significant aspect of an embodiment is the possibility of recording an optical identification element of a particular slide or perhaps merely recording information relevant to an element. Such information may include information concerning the tissue sample, of course. Similarly, optical identification may be recorded on a reagent container that may include information concerning the reagent contained therein. It may provide for recording a two-dimensional symbology on a slide or even on a reagent container. Two-dimensional symbology recorded on a slide may represent data including, but not limited to: tissue sample related data, patient identification data, staining protocol data, or the like. Two-dimensional symbology recorded on a reagent container may represent data including, but not limited to: reagent related data, reagent type data, reagent volume related data, reagent durability related data, or the like. It may also provide a connection element through which captured image data may be transferred to the control element. It may include feeding the image data to a control element so that the robotic element may respond. After the relevant image data has been recorded, and perhaps as a result of feeding that data to the control element, the invention may manipulate a staining or other process according to that relevant image data. Thus the invention may perform staining of slides according to tissue specific protocols.

The staining apparatus 1 of the present embodiment further comprises a probe washing station 8 and a reagent mixer 9, and the robotic element 20 is furthermore arranged to transfer the probe to the washing station 8 as well as to the reagent mixer 9.

As shown in fig. 4, the reagent bottle 3 may be provided with an area 30 on a surface on which to mount an optical identification element. This optical identifier may be an

adhesive label 31 carrying encoded information about the content of the bottle 3, such as reagent type, date of manufacture, expiry date, etc. The encoded information could be in the form of a data matrix code, an Infoglyph code or any other kind of 2-D code, and could in principle also be a simple 1-D code, i.e. a bar code. Additionally, the label 31 may also be provided with human readable text to aid the operator handling the reagent bottles e.g. during loading of bottles into the staining apparatus.

Fig. 5 shows a slide 7 with a label 71 mounted thereon. One layout of the label 71 is shown in fig. 6. The label 71 may be an adhesive optical identifier, which may be prepared for the particular slide and printed on a label printer (not shown) or any other suitable printing device. It is even possible that in a particular situation, if a batch of slides is to be subjected to the same treatment, a series of identical labels could be provided for the slides. The label 71 may comprise an area 72 for encoded information about the tissue sample on the slide 7, such as patient data, date and file number, the staining protocol and/or the series of process steps. Furthermore, the label 71 may be provided with one or more rows 73 of human readable text and/or blank space for the laboratory personnel preparing the slides to write on the slide label.

In figures 7 to 9 various kinds of data encoded symbology for the label 71 (the entire label 71 as shown or only for the label area 72 (see fig. 6)).

In fig. 7, an example of a 2-D symbology of the Infoglyph™ type is shown. This may include perhaps even an information carpet type of symbology. This type of 2-D symbology is advantageous since it can carry a large amount of optically machine-readable information. Making use of a high-resolution camera, this type of symbology may be readable in a high resolution and a large amount of information can be encoded therein. The symbology may be printed with tiny diagonal lines in

different directions or perhaps even colors and can easily be read by a CCD camera or the like.

Fig. 8 shows an example of a data matrix code that can be used as an alternative to the Infoglyph symbology. The data matrix is similarly readable with a CCD camera but may not carry as many data in the encoding as the Infoglyph. However, it is easier to print as it may have a less high resolution making it a simple and cost effective solution if less identification data on the slides and the reagent bottles is required. A yet simpler solution is shown in fig. 9, where the symbology is the old bar code. In principle this means that only a bar code scanner is required for reading the slides and the reagent bottle information, but by using a 2-D sensor, the possibility of self-calibration and monitoring the installation of slides and reagents in the staining apparatus may be enhanced.

In an embodiment, the optical identifiers on the slides and on the reagent bottles are the same type. This may facilitate the image processing of the identification process in the staining apparatus.

A different approach to identifying the individual slides or as a way of facilitating the new capabilities of confirming identification or storing confirmatory information may be to record the contour and/or the texture of the tissue sample 74 itself, such as shown in fig. 10. Utilizing the high-resolution of the image that can be recorded by the camera, the unique features of the tissue sample itself can be used as a graphical identifier of the slide. Furthermore, an image of the stained tissue sample can be recorded so that a digital representation of the tissue sample is produced. This digital image can be sent electronically to remote locations for instant examination and/or archived for later examination. This may provide the staining apparatus with a unique flexibility in use and may introduce new and advantageous methods of analyzing the tissue samples.

Besides identifying the microscope slides and the reagent bottles in the staining apparatus, the 2-D optical sensor can also be used for self-calibration of the apparatus, e.g. after maintenance, if the apparatus has been disassembled or moved to another location. By identifying critical locations within the apparatus by capturing an image by the camera, the image processing software can compare the captured image with a reference image to determine if certain critical components in the apparatus are off-set from their predetermined positions, e.g. if a slide rack or a slide is slightly off-set, and if so, a set of correction data for the robotic motion control system may be calculated and this set of data may be used for calibrating the apparatus. If the correction needed exceeds a certain size, a warning could be automatically issued to an operator, so that it is ensured that the apparatus does not malfunction during the processing of the slides. Furthermore, this image analysis system could also be used for determining if a slide is present or dislocated in the rack in order to produce a warning signal.

By the invention, it is realised that a variety of changes of the above description of some preferred embodiments of the invention may be made without departing from the scope of the invention as set forth in the claims. As can be easily understood, the basic concepts of the present invention may be embodied in a variety of ways. It involves both staining techniques as well as various systems, assemblies, and devices to accomplish staining and other functions. In this application, the staining techniques are also disclosed as part of the results shown to be achieved by the various systems, assemblies, and devices described and as steps that are inherent to utilization. They should be understood to be the natural result of utilizing the devices as intended and described. In addition, while some devices are disclosed, it should be understood that these not only accomplish certain methods but also can be varied in a number of ways. Importantly, as to all of the foregoing, all of these facets should be understood to be encompassed by this disclosure.

The reader should be aware that the specific discussion may not explicitly describe all embodiments possible; many alternatives are implicit. It also may not fully explain the generic nature of the invention and may not explicitly show how each feature or element can actually be representative of a broader function or of a great variety of alternative or equivalent elements. Again, these are implicitly included in this disclosure. Where the invention is described in device-oriented terminology, each element of the device implicitly performs a function. Apparatus claims may not only be included for the device described, but also method or process claims may be included to address the functions the invention and each element performs. Neither the description nor the terminology is intended to limit the scope of the disclosure.

It should also be understood that a variety of changes may be made without departing from the essence of the invention. Such changes are also implicitly included in the description. They still fall within the scope of this invention. A broad disclosure encompassing both the explicit embodiment(s) shown, the great variety of implicit alternative embodiments, and the broad methods or processes and the like are encompassed by this disclosure and may be relied upon to support additional claims for presentation in this or subsequent patent application.

Further, each of the various elements of the invention and claims may also be achieved in a variety of manners. This disclosure should be understood to encompass each such variation, be it a variation of an embodiment of any apparatus embodiment, a method or process embodiment, or even merely a variation of any element of these. Particularly, it should be understood that as the disclosure relates to elements of the invention, the words for each element may be expressed by equivalent apparatus terms or method terms -- even if only the function or result is the same. Such equivalent, broader, or even more generic terms should be considered to be encompassed in the description of each element or action. Such terms can be substituted where desired to make explicit the implicitly broad coverage to which this invention is entitled. As but one example, it should be understood that

all actions may be expressed as a means for taking that action or as an element which causes that action. Similarly, each physical element disclosed should be understood to encompass a disclosure of the action which that physical element facilitates. Regarding this last aspect, as but one example, the disclosure of a "sensor" should be understood to encompass disclosure of the act of "sensing" -- whether explicitly discussed or not -- and, conversely, were there effectively disclosure of the act of "sensing", such a disclosure should be understood to encompass disclosure of a "sensor" and even a "means for sensing". It should also be understood that in jurisdictions where specific language may be construed as limiting, as but one example in the United States where some interpretations of "means for" elements can be construed narrowly, broader equivalent language (such as " element" or the like) may be used to avoid the narrow interpretation and should be understood as encompassed by this specification. Such changes and alternative terms are to be understood to be explicitly included in the description.

Any patents, patent applications, publications, or other references mentioned in this application for patent are hereby incorporated by reference. In addition, as to each term used it should be understood that unless its utilization in this application is inconsistent with such interpretation, common dictionary definitions should be understood as incorporated for each term and all definitions, alternative terms, and synonyms such as contained in the Random House Webster's Unabridged Dictionary, second edition are hereby incorporated by reference. Finally, any priority case for this application is hereby appended and hereby incorporated by reference.

Thus, the applicant(s) should be understood to have support to claim at least: i) each of the sample processing systems and subsystems as herein disclosed and described, ii) the related methods disclosed and described, iii) similar, equivalent, and even implicit variations of each of these systems, assemblies, devices and methods, iv) those alternative designs which accomplish each of the functions shown as are

disclosed and described, v) those alternative designs and methods which accomplish each of the functions shown as are implicit to accomplish that which is disclosed and described, vi) each feature, component, and step shown as separate and independent inventions, vii) the applications enhanced by the various systems or components disclosed, viii) the resulting products produced by such systems or components, and ix) methods and systems, assemblies, devices, and apparatuses substantially as described hereinbefore and with reference to any of the accompanying examples, x) the various combinations and permutations of each of the elements disclosed, xi) each potentially dependent claim or concept as a dependency on each and every one of the independent claims or concepts presented, xii) processes performed with the aid of or on a computer as described throughout the above discussion, xiii) a programmable system as described throughout the above discussion, xiv) a computer readable memory encoded with data to direct a computer comprising means or elements which function as described throughout the above discussion, xv) a computer configured as herein disclosed and described, xvi) individual or combined subroutines and programs as herein disclosed and described, xvii) the related methods disclosed and described, xviii) similar, equivalent, and even implicit variations of each of these systems and methods, xix) those alternative designs which accomplish each of the functions shown as are disclosed and described, xx) those alternative designs and methods which accomplish each of the functions shown as are implicit to accomplish that which is disclosed and described, xxi) each feature, component, and step shown as separate and independent inventions, and xxii) the various combinations and permutations of each of the above.

Further, if or when used, the use of the transitional phrase "comprising" or the like is used to maintain the "open-end" claims herein, according to traditional claim interpretation. Thus, unless the context requires otherwise, it should be understood that the term "comprise" or variations such as "comprises" or "comprising" or the like, are intended to imply the inclusion of a stated element or step or group of elements or steps but not the exclusion of any other element or step or group of

elements or steps. Such terms should be interpreted in their most expansive form so as to afford the applicant the broadest coverage legally permissible.

Any claims set forth at any time are hereby incorporated by reference as part of this description of the invention, and the applicant expressly reserves the right to use all of or a portion of such incorporated content of such claims as additional description to support any of or all of the claims or any element or component thereof, and the applicant further expressly reserves the right to move any portion of or all of the incorporated content of such claims or any element or component thereof from the description into the claims or vice-versa as necessary to define the matter for which protection is sought by this application or by any subsequent continuation, division, or continuation-in-part application thereof, or to obtain any benefit of, reduction in fees pursuant to, or to comply with the patent laws, rules, or regulations of any country or treaty, and such content incorporated by reference shall survive during the entire pendency of this application including any subsequent continuation, division, or continuation-in-part application thereof or any reissue or extension thereon.

CLAIMS

What is claimed is:

1. An automatic staining apparatus comprising:

at least one reagent container positioned within a reagent section;

at least one sample;

at least two staining sections separated by the reagent section;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive; and

an image-capture 2-D optical sensor configured to two dimensionally image at least one element in said automatic staining apparatus.

2. An apparatus according to claim 1, wherein the optical sensor is adapted to locate pre-selected reference features for self-calibration of the robotic element.

3. An apparatus according to claim 1 or 2, wherein the optical sensor is adapted to record an image of the finalised sample after said sample has been subjected to a staining protocol.

4. An apparatus according to claim 1, wherein at least one element comprises an element selected from a group consisting of: a two-dimensional high-resolution symbology code, a datamatrix code, a bar code, an adhesive label, a two dimensional symbology zone, and a human readable text zone; and wherein the optical sensor is adapted to record an image of the finalised sample after said tissue sample has been subjected to a staining protocol.

5. An apparatus according to claim 1, wherein the optical sensor is configured to identify a feature selected from a group consisting of: the texture of the sample, the outline of the sample, a visual property of the sample, and an individual identification feature of the sample; and wherein the optical sensor is adapted to record an image of the finalised sample after said sample has been subjected to a staining protocol.

6. A method of identifying at least one property in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

optically sensing a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data;

recording robotic element calibration reference points in the apparatus; and

feeding said image data to a control element to which said robotic element is responsive.

7. A method of staining samples in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing slides in racks;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

providing an optical sensor responsive to said robotic element and adapted to sense a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data;

recording robotic element calibration reference positions for said racks; and

feeding said image data to a control element to which said robotic element is responsive.

8. An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive; and

an optical sensor adapted to locate pre-selected reference features for self-calibration of the robotic element.

9. An automatic staining apparatus comprising:

at least one reagent container in a reagent section;

at least one first sample contained on a slide in a first slide section;

at least one second sample contained on a slide in a second slide section, wherein said first slide section and said second slide section are separated by said reagent section;

a robotic element adapted to affect said reagent container and said first and said second samples; and

a control element to which said robotic element is responsive.

10. An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive; and

an image-capture 2-D optical sensor configured to two dimensionally image at least one element in said automatic staining apparatus, wherein said at least one element comprises an optical identification element having reiterated information.

11. An apparatus according to claim 10 wherein said reiterated information comprises multiple reiterated information.

12. An apparatus according to claim 10 wherein said reiterated information comprises redundant information.

13. An apparatus according to claim 10, 12 wherein said at least one element comprises an optical identification element.

14. An apparatus according to claim 11 wherein said optical identification element comprises a two-dimensional high-resolution symbology code.

15. An apparatus according to claim 11 wherein said optical identification element comprises a datamatrix code.

16. An apparatus according to claim 11 wherein said optical identification element comprises a bar code.

17. An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said tissue sample;

a control element to which said robotic element is responsive;

an image-capture 2-D optical sensor configured to two dimensionally image at least one element in said automatic staining apparatus; and

a computer image biological analysis element.

18. An apparatus according to claim 17 wherein said optical sensor comprises a camera.

19. An apparatus according to claim 18, wherein said camera comprises a CCD element.

20. An apparatus according to claim 17, wherein the samples comprises biological samples accommodated on slides.

21. A method of identifying at least one property in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

optically sensing a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data;

feeding said image data to a control element to which said robotic element is responsive; and

biologically analysing image data of said at least one sample with a computer.

22. A method according to claim 21, wherein said step of optically sensing the two dimensional image of at least one element in said automatic staining apparatus comprises the step of utilizing a camera.

23. A method according to claim 22, wherein said step of utilizing a camera comprises the step of utilizing a CCD element.

24. A method according to claim 21, 22 or 23, wherein said step of providing at least one sample comprises the step of utilizing a slide.

25. A method of staining tissue samples in an automatic staining apparatus comprising the steps of:

providing at least one sample;

providing at least one reagent container;

providing a robotic element adapted to affect said reagent container and said sample;

providing an optical sensor responsive to said robotic element and adapted to sense a two dimensional image of at least one element in said automatic staining apparatus;

recording relevant image data;

feeding said image data to a control element to which said robotic element is responsive; and

biologically analysing image data of said at least one sample with a computer.

26. A method according to claim 25, wherein said step of providing at least one sample comprises the step of utilizing a slide.

27. A method according to claim 25 or 26, wherein said step of providing an optical sensor comprises the step of utilizing a camera.

28. A method according to claim 25 or 26, wherein said step of providing an optical sensor comprises the step of utilizing a CCD element.

29. A method according to claim 25, and further comprising the step of storing an image relevant to a process of staining tissue samples.

30. An automatic staining apparatus comprising:

at least one reagent container;

at least one sample;

a robotic element adapted to affect said reagent container and said sample;

a control element to which said robotic element is responsive;

a multifunction optical sensor configured to sense at least one element in said automatic staining apparatus; and

a computer image biological analysis element.

31. An apparatus according to claim 30, wherein said at least one sample comprises at least one sample accommodated on slides.

32. An apparatus according to claim 30, wherein said optical sensor comprises a camera.

33. An apparatus according to claim 30, wherein said optical sensor comprises a CCD element.

34. An apparatus according to claim 30, and further comprising a stored image relevant to the process of staining tissue samples.

ABSTRACT

The present invention concerns an apparatus for automatic staining of tissue samples, said apparatus perhaps including a reagent section or reagent containers; at least one staining section or tissue samples, a robotic head or robotic element that may move reagent to a predetermined tissue sample, said robotic element being moveable above the reagent and the staining sections, a control element that may manage a staining process, a 2-D optical sensor to detect two-dimensional image data of a relevant property and that can feed the captured image data to the control element. By providing the robotic element with a 2-D optical sensor, a common image processor may be provided having multiple functions. By using a 2-D optical image processing system, the control system of the apparatus may easily be adapted to read various types of data presentations, just as actual images for sections of the apparatus may be identified in order to assess the condition of the apparatus. The optical sensor may be used to automatically identify the slides and the reagent containers present in the apparatus, just as the optical sensor may be used for checking if a slide is misplaced at or absent from a certain slide position, etc.

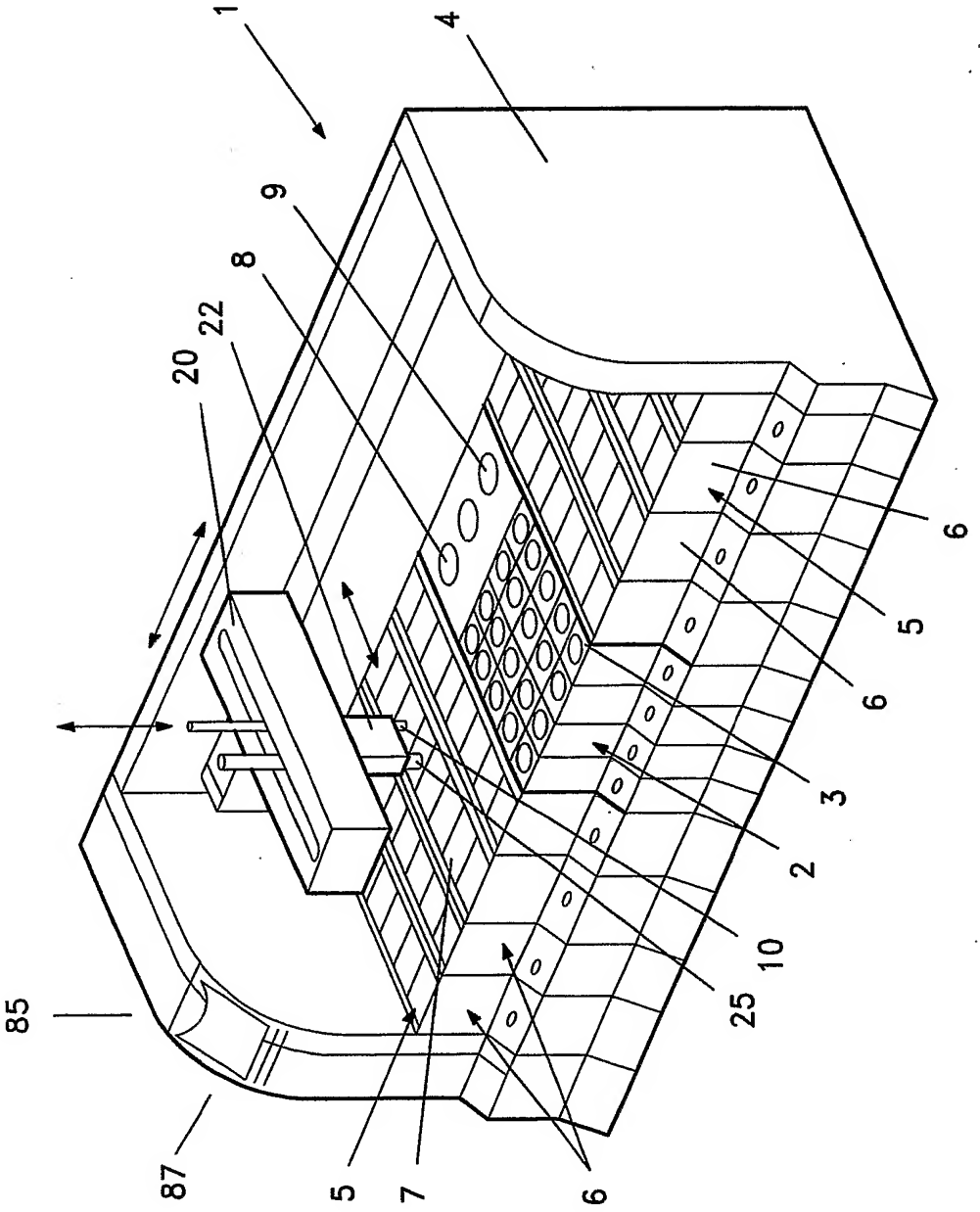

Fig. 1

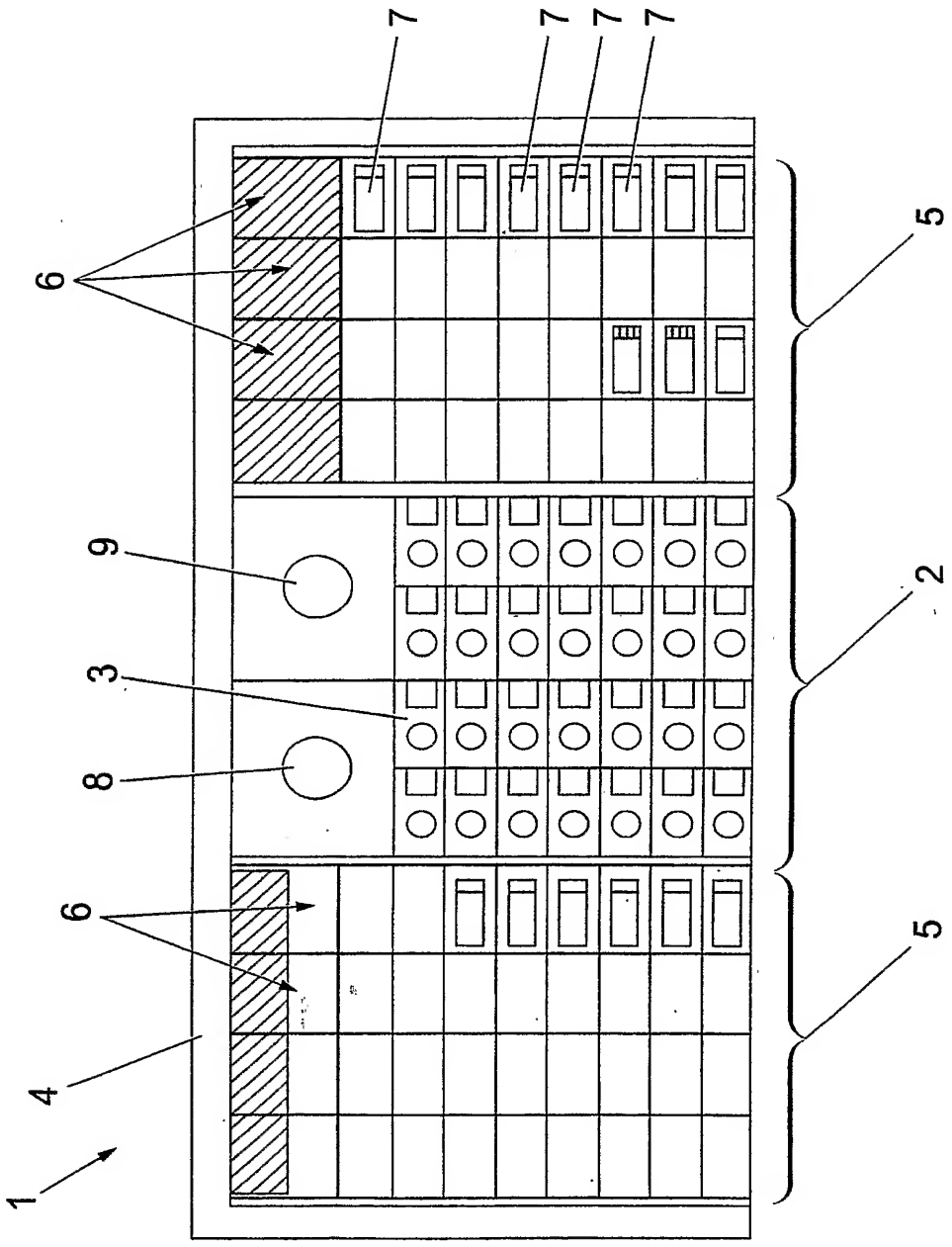

Fig. 2

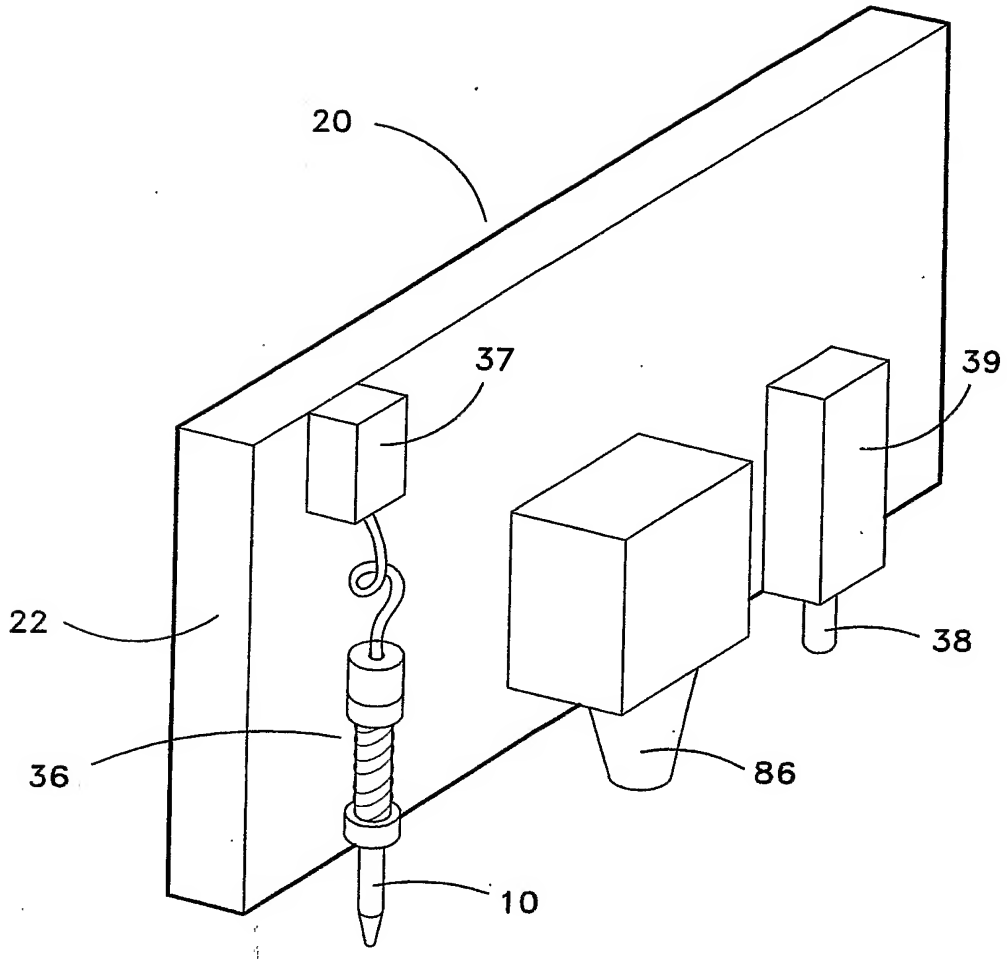

Fig. 3

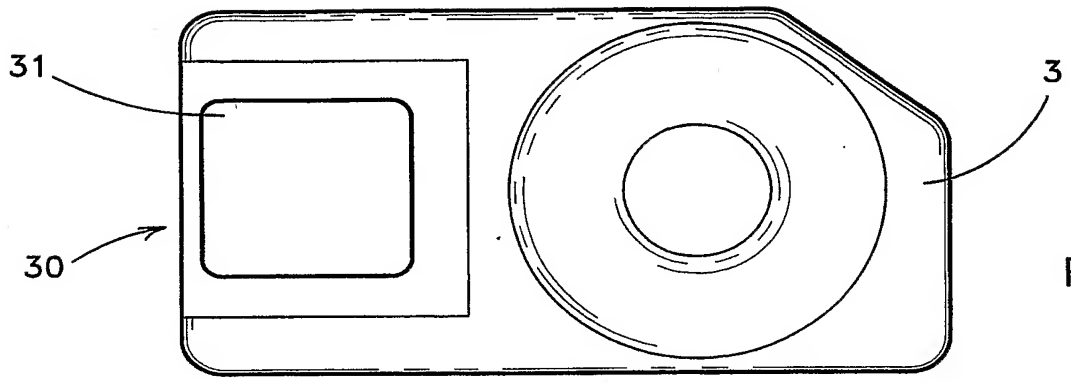

Fig. 4

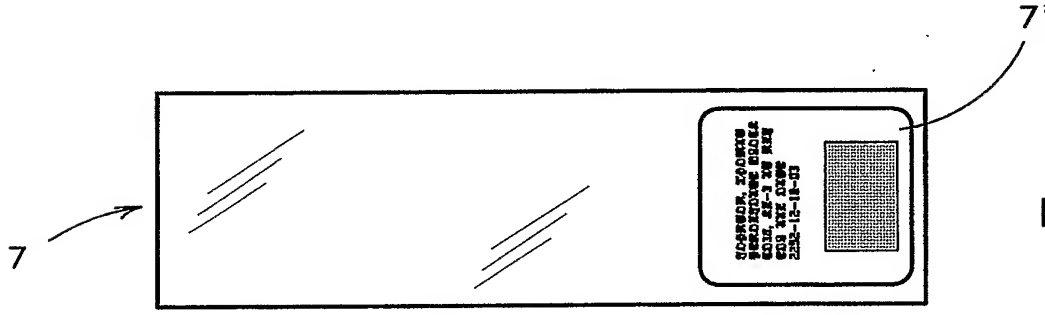

Fig. 5

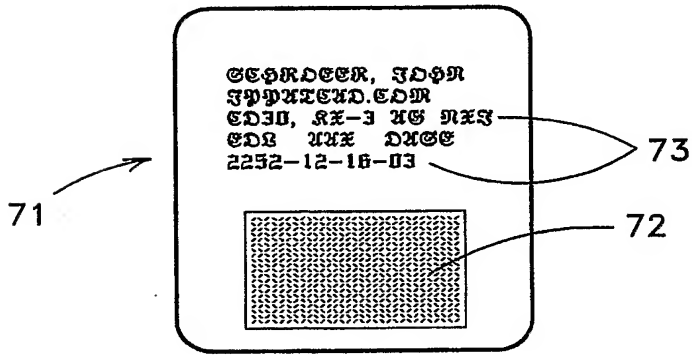

Fig. 6

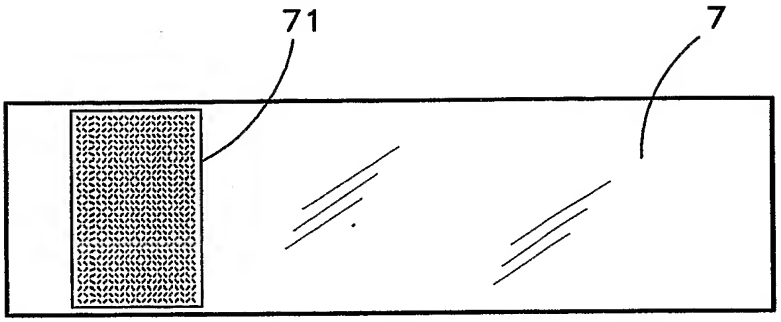

Fig. 7

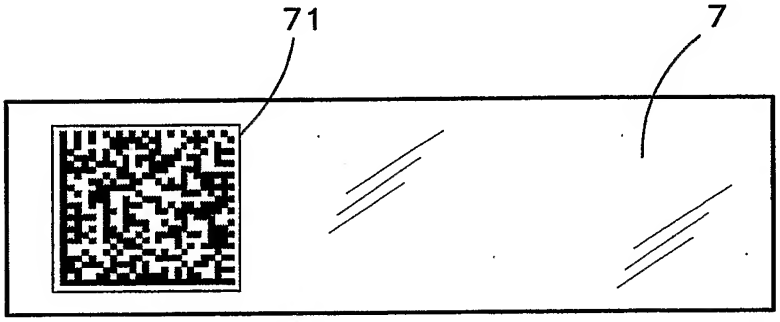

Fig. 8

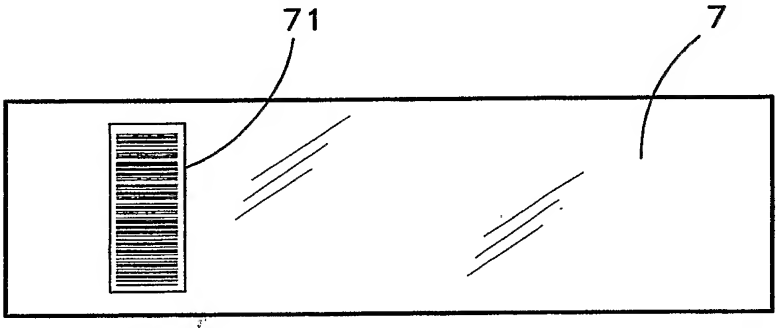

Fig. 9

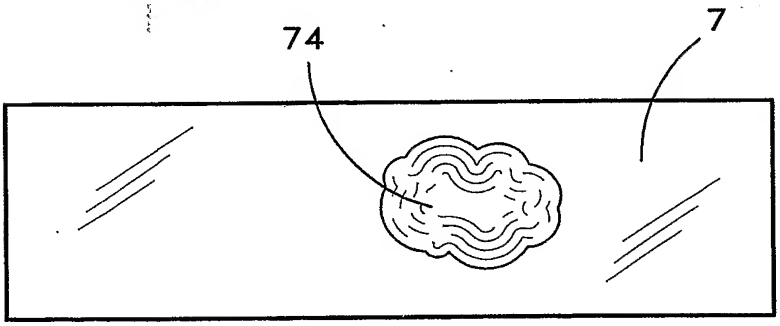

Fig. 10